THE ACTION OF EXTRACTS OF THE PITUITARY BODY

BY

H. H. DALE, M.A., M.D.

(Reprinted from the *Journal of Pharmacology*, Vol. IV, No. 3, 1909)

From the Wellcome Physiological Research Laboratories
Brockwell Hall
Herne Hill
London, S.E.

THE ACTION OF EXTRACTS OF THE PITUITARY BODY

By H. H. DALE, M.A., M.D.

From the Wellcome Physiological Research Laboratories, Herne Hill, London, S.E.

(*Received October 1st, 1909*)

I. Introductory

Though the activity of pituitary extracts was discovered by Oliver and Schäfer (1) almost simultaneously with that of suprarenal extracts, the conceptions of the nature of the action of the former are as yet far less precise. A comparison of the two was inevitable, and it has more than once been suggested that their action, at least as regards vaso-constriction, is of the same kind and produced by stimulation of the same structures. Herring (2) advanced this view as regards the arteries: a more recent observation by Cramer (3), of the action of pituitary extract on the pupil of the frog's eye (enucleated), lends support to the same idea: still more recently an account given by Bell and Hick (4) of the action on the uterus emphasised the similarity between the action of extracts from the two organs. I thought it worth while, therefore, to bring together a number of observations, made at different times and in different connexions, which appear to me to indicate that such correspondence as exists is wholly superficial and illusory. In the first place it must be admitted that the actions of pituitary and suprarenal extracts have superficially several points of suggestive similarity. Both raise the blood-pressure, peripheral vaso-constriction being a principal factor in the effect (Oliver and Schäfer): in both cases the active principle is limited to a small, morphologically independent portion of the gland, developmentally related to the central nervous system in the one case, as to the sympathetic system in the other. Attention is drawn to these points of similarity by Schäfer and Herring (5), who state that 'here the parallelism ends': but the divergence of which they make specific mention is that the pituitary extract has an additional effect on the kidney. Since they attribute this to a separate active principle, no true divergence is indicated between the *pressor* principles of the two organs. It has been shown (Langley (6), Brodie and Dixon (7), Elliott (8)) that the action of adrenaline reproduces with striking accuracy the effects of stimulating nerves of the true

sympathetic or thoracico-lumbar division of the autonomic system. An examination of the action of pituitary extract on various organs and systems containing plain muscle and gland-cells will indicate whether its action has more than a superficial resemblance to that of adrenaline by showing whether its effects, or any group of them, can be similarly summarised by relating them to a particular element of the visceral nervous system. Incidentally evidence will be discussed which throws light on the contention of Schäfer and Herring that two active principles exist in the extract, one acting on the circulatory system, the other specifically on the kidney.

The extract used in my experiments, except where otherwise stated, was a 5 per cent. decoction of the fresh posterior lobes of ox pituitaries. The posterior lobes were dissected clean from the rest of the gland and from dura water, weighed in the moist condition, pounded with sand, and boiled with water faintly acidulated with acetic acid to produce coagulation. The extract, filtered from coagulum, is a clear colourless fluid giving a faint biuret reaction. For experiments on isolated organs the extract was prepared with Ringer's solution and carefully neutralised before use.

II. The Effect on the Circulatory System

It has been mentioned that pituitary extract causes a striking rise of blood-pressure, chiefly due to arterial constriction. If the action had any relation to innervation by the sympathetic system we should expect to find that the effect on the arteries was accompanied by an increased frequency and force of the heart-beat, corresponding to the effect of the cardio-accelerator nerves. It was pointed out by Schäfer and Oliver that this was not the case: the beat of the heart usually becomes slower, even after exclusion of vagus action, though it may be somewhat augmented. Reference will be made later to the action of the extract on the isolated heart, which enables the effect to be studied in its least complicated form.

We should further expect to find, if the action were like that produced by sympathetic nerve-impulses, that the action on the arteries showed irregularities of distribution corresponding to that of sympathetic nerves. It was of special interest, therefore, to examine the action on those arteries which have been shown to be exceptional in their innervation and in their reaction to adrenaline.

The pulmonary arteries. Brodie and Dixon showed that the peripheral branches of the pulmonary artery are exceptional in that their

muscular coats are not under the control of sympathetic nerves, and made the interesting parallel observation that adrenaline, perfused through the pulmonary vessels, produces no vaso-constrictor but a small vaso-dilator effect. With segments of the main branches of the pulmonary artery, treated as isolated organs, others have obtained definite constrictor effects with adrenaline (Meyer (9), Langendorff (10)). It is clear that there is no real discrepancy between the two sets of observations: the only conclusion justified by the evidence is that the sympathetic nerves send motor fibres to the muscular walls of the pulmonary artery and its main branches, but that the innervation stops short of the peripheral arterioles, the calibre of which is alone concerned in determining the rate of perfusion under constant pressure, as measured by Brodie and Dixon.

In a few experiments with isolated rings of large branches of the pulmonary arteries of large dogs and goats, I observed contraction on adding small quantities of the pituitary extract to the Ringer's solution in which the rings were suspended. Since these experiments were made similar observations have been published by de Bonis and Susanna (11). Since, however, I obtained even more pronounced constriction of the strips of pulmonary artery on adding adrenaline, these results only add another to the cases already known in which adrenaline and pituitary extract both cause constriction of an artery, and are of no significance for our present enquiry. I owe to Professor Dixon the opportunity of making with him observations on the effect of pituitary extract on the peripheral pulmonary arterioles. The observations were made in connection with experiments concerning action on these arterioles of certain organic bases. The lungs were perfused with Ringer's solution, or defibrinated blood diluted therewith, according to the method described by Brodie and Dixon. After it had been shown that either adrenaline or p. hydroxyphenyl-ethylamine caused only a slight acceleration of the rate of perfusion, 1 c.c. of the pituitary extract was introduced into the circulating fluid. As soon as the extract reached the lungs there was a pronounced retardation of the outflow. The observation was repeated several times, in different experiments, with uniform result. Here, then, is a clear case of vaso-constriction produced by pituitary extract on a system in which no such constriction is produced by adrenaline or substances of similar action.

The coronary arteries. The innervation of the coronary arteries cannot be regarded yet as definitely settled, even the more recent observations being by no means concordant. Maas (12) found that the vagus supplies vaso-constrictor fibres to this system: Dogiel and

Archangelsky (13) found that vaso-constrictor fibres are contained in the accelerator nerves: on the other hand Schäfer (14) could not find any evidence for vaso-motor nerves to these arteries, and observed no constriction of them under the influence of adrenaline. The last observation was confirmed by Elliott (8), who found the outflow from a perfused segment of ventricle increased by adrenaline. Langendorff observed that adrenaline caused relaxation of an isolated ring of coronary artery, and this has been confirmed by de Bonis and Susanna. Still more recently Wiggers (15) has found evidence of vaso-constriction when adrenaline is added to a fluid perfusing the coronary arteries. From all this conflicting evidence emerge the facts that the coronary arteries are slightly, if at all, controlled by vaso-motor nerves, and that the constrictor effect of adrenaline on the peripheral branches, if it exist at all, is very weak compared with the effect of that principle on other arteries.

In this instance I made no experiments with isolated rings of artery, but such have recently been published by Pal (16) and by de Bonis and Susanna. These observers agree in finding that pituitary extract causes a marked constriction of a ring cut from a large coronary artery. De Bonis and Susanna also confirmed Langendorff's observation that adrenaline causes relaxation of such a ring, so that in this case the action of the two principles is again contrasted.

My own experiments were made with the isolated heart of the rabbit, perfused with oxygenated Locke-Ringer solution, by Langendorff's method as modified by Locke. There are several errors involved in the measurement of the coronary outflow from such a preparation. These have recently been discussed by Wiggers. The outflowing Ringer's fluid always accumulates to a certain extent in the right auricle and ventricle, and, as Schäfer pointed out, a certain amount may pass the semi-lunar valves and so reach the left ventricle. With small hearts I have not found that these defects seriously disturb the *average* rate of outflow: the principal drawback is that the dripping of the fluid from the heart is rendered irregular by the accumulation of fluid in the right side of the heart during diastole, and its ejection by the systole. With a small, rapidly-beating heart the quick and irregular succession of small drops which results can be averaged and converted into a regular series of large drops by a simple device. I used a large glass funnel, placed immediately beneath the recording lever. A skein of threads, hanging loosely from the heart and lever into the mouth of the funnel, ensured the delivery

into it of all the fluid leaving the heart, without at all interfering with the record of the contractions. The funnel was fixed in an inclined position and over the lower opening of the stem was drawn a short length of rubber tubing, the diameter of which could be reduced by a clip. This device converts an irregular series of drips and splashes into a regular series of large drops, which fall at a constant rate so long as the average rate of the drippings from the heart remains constant. These large drops were recorded on the smoked drum by the ordinary arrangement of receiving and recording tambours. When the beat of the heart and the rate of the coronary outflow, as shown by the drop recorder, had become constant, a small quantity of the filtered and warmed pituitary extract was introduced into the bulb of the heart-cannula by means of a hypodermic syringe, the needle being thrust through the wall of the rubber tube leading to the cannula. Fig. 1 shows a typical effect. It will be seen that the outflow from the coronary sinus becomes very much slower as soon as the extract reaches the heart. The effect shown in the figure is quite typical, and I know of no other drug which, in doses not immediately fatal to the heart-muscle itself, will produce so pronounced a constriction of the coronary arteries. That the effect is genuinely due to constriction, and not to viscosity or mechanical accident, can easily be ascertained from the fact that a second dose, introduced when the effect of the first has subsided, produces a very small change in the rate of outflow. This is quite in accordance with the observation, first made by Howell (25), that a second dose of the extract, given intravenously when the effect of a first large dose has passed off, produces hardly any rise of arterial blood-pressure.[1]

One other point needs mention. It is clear from what has been said above that a weakening or stoppage of systole might lead to an apparent temporary retardation of the coronary outflow by allowing accumulation in the right side of the heart. The phenomenon illustrated is not of that kind. It is a prolonged effect, which persists to some degree for upwards of half an hour after the injection, and its maximum coincides with a phase of increased ventricular activity. There is no room for doubt, therefore, that the coronary arterioles afford another example of an arterial area slightly, if at all affected by adrenaline, stimulated to intense constriction by pituitary extract.

The effect on the ventricular beat of the isolated heart

1. It is of interest to note that Dr. W. H. Harvey, to whom I communicated my observation of the constricting effect of pituitary extract on the coronary arteries, has produced sclerotic changes in these arteries by repeated injections of the extract.

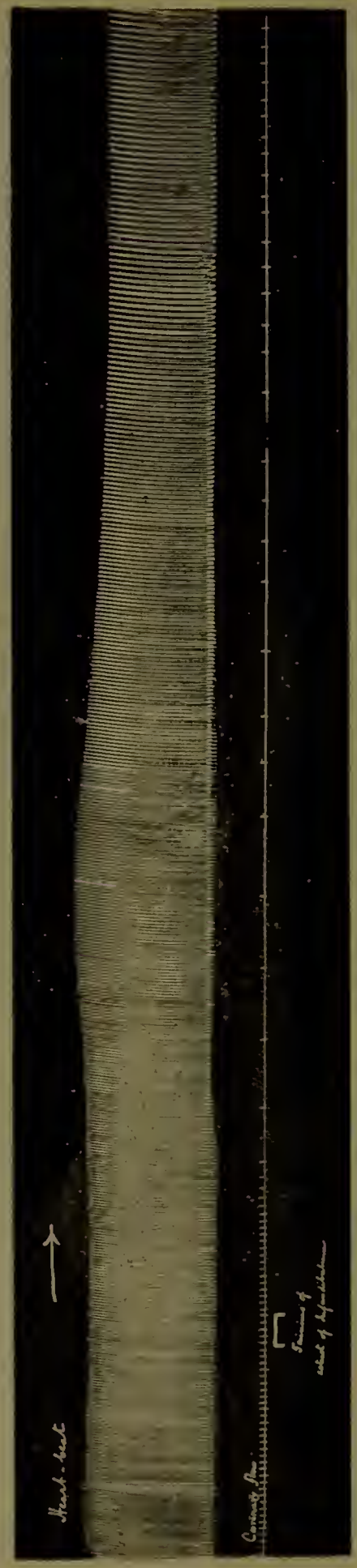

Figure 1.—Ventricular beat and flow through coronary vessels of the isolated heart of a rabbit. Effect of adding 5 minims of pituitary extract to the perfusing Locke-Ringer solution. Scale ½ linear.

can also be studied in fig. 1. It will be seen that, immediately after the injection, it becomes slightly slower and considerably more vigorous: later, with persistent retardation, it becomes weaker than before the injection. Similar effects, in the same order, have been previously described by Hedbom (17) and by Cleghorn (18). It is difficult, however, to decide how far these changes in ventricular activity are due to primary action on the cardiac muscle, how far to reduction of the oxygen supply by coronary constriction. Neither effect is modified by previous atropinisation, so that there can be no question of the peripheral vagus-mechanism being concerned. There is further, in the case of the effect on the heart-beat, as in that of the coronary constriction, no resemblance whatever to the effect of accelerator nerves or of adrenaline. The safest conclusion is to regard the action on the coronary arteries as certainly a primary effect of the extract, that on the heart-beat as probably in part due to direct effect on the heart-muscle, and in part secondary to the altered rate of coronary perfusion. It should be noted, in this connection, that under conditions of natural circulation, in which the effect of coronary constriction would be antagonised by the great rise of systemic pressure, the secondary weakening of the beat is not usually observed.

The renal arteries. Schäfer with Magnus (19), and later with Herring (5), found that the kidney expanded when pituitary extract was injected intravenously. It was of interest, therefore, to examine the effect of pituitary extract on the rate of perfusion through the renal vessels. The perfusion was made with oxygenated Ringer's solution under constant pressure, as for the isolated heart, the outflow from the renal veins being measured by the drop-counter. The kidneys used were those of cats and dogs. Both kidneys of the cat were perfused, the cannulae being inserted into segments of aorta and vena cava. From the dog one kidney was used, with cannulae in the renal artery and vein. The pituitary extract was added by injection into the circulating Ringer's fluid. The following results were obtained:—

	Injection of Pituitary Extract		Rate of Outflow in Drops per 20 seconds	
			Before injection	After injection
Experiment I.—Cat.		5 minims	34	20
Experiment II.—Cat.	1st.	5 minims	39	27
	2nd.	10 minims	29	31
Experiment III.—Dog.	1st.	5 minims	24	20
	2nd.	10 minims	20	22

It will be seen that the first injection causes in each case a decided though small constriction. The genuineness of the phenomenon is again shown by the failure of second injections, which even slightly reduce the resistance of the constricted arteries. Similar results were obtained by Houghton and Merrill (24), in the course of experiments made to determine whether the extract locally excites the renal epithelium to secretion. On the other hand Pal states that isolated rings of the proximal portion of the renal artery were constricted, while rings from more peripheral portions were relaxed by the extract. On the whole the evidence obtained with isolated organs suggests that the marked swelling of the kidney in its natural relations must be chiefly due to a relative insensitiveness of the renal arteries towards the vaso-constrictor effect of the extract. It might seem, at first sight, that even this implied, as Pal concludes, an action of the vaso-constrictor principle on some nervous structure, and not on the muscular coats of the arteries themselves. This, however, is by no means the only instance of an exceptional reaction of the renal arteries towards general stimulants of plain-muscle contraction. The various drugs of the digitalis series, for example, injected in small doses, cause expansion of the kidney and diuresis, especially in the rabbit; but the result of most experiments on the artificial perfusion of these drugs through the vessels of the excised kidney, especially of the dog and the cat, has been to demonstrate a marked constrictor action even on the vessels of that organ. There is no reason at all for supposing that these drugs act on nervous structures, and there is as little in the case of the pituitary extract. The anomalous reaction of the kidney vessels in their natural relations is clearly a similar phenomenon to their reaction to the digitalis series; but since the pituitary extract acts more powerfully on the arterioles and less on the heart than digitalis and its allies, the phenomenon is presented by the former in an exaggerated form.

The Spleen. The spleen may be regarded, in so far as its contractile activity is concerned, as belonging to the circulatory system. Schäfer and Magnus showed that pituitary extract caused contraction of the muscular capsule. I have repeated this observation with a like result. A plethyomographic record of the effect is shown in fig. 2.

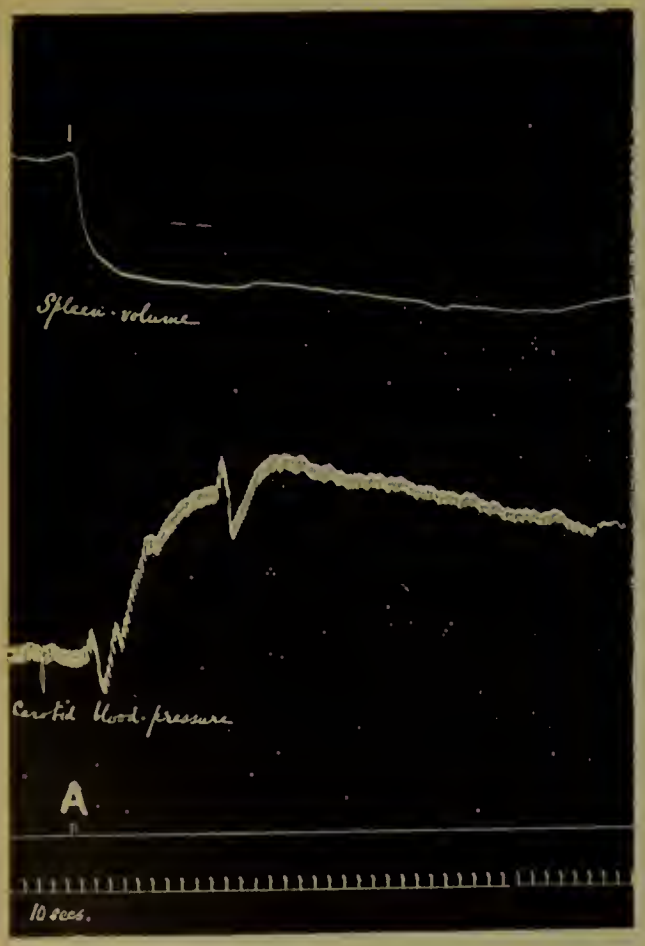

Figure 2.—Spleen volume and carotid blood-pressure of pithed cat. At A, 1 c.c. of pituitary extract injected intravenously. Signal line = zero of blood-pressure. Scale, ½ linear.

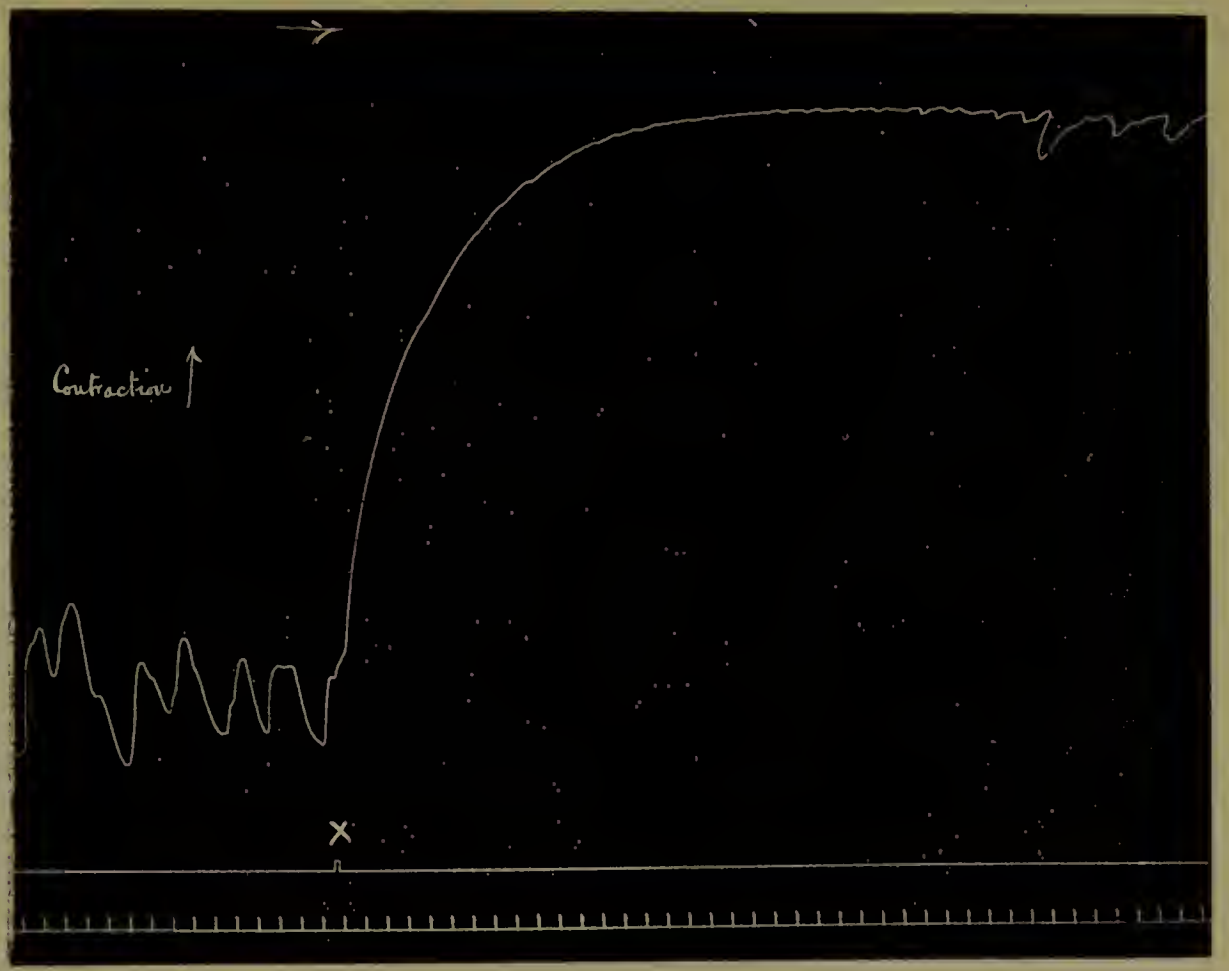

Figure 3.—Contractions of isolated horn of cat's uterus (not pregnant). At × 3 drops of pituitary extract were added to the 200 c.c. of Ringer's solution in the bath. Time = 10 seconds. Scale, ½ linear.

III. The Uterus

In a paper on another subject (22) I mentioned incidentally the powerful uterine contraction produced by pituitary extract. I have since extended the observation, finding, as expected, that the action, like that on the arteries, is possessed by extracts of the posterior lobe only.

Bell and Hick, working with the extract which I myself used, appear to have obtained a comparatively small effect on the rabbit's uterus in the resting (i.e., non-pregnant and non-oestrous) condition. This is quite contrary to my own experience. They worked exclusively with the rabbit. This animal is not really suitable, however, for our present enquiry, since its uterus responds, under all conditions, to the stimulus of sympathetic nerves or adrenaline, by contraction. In the cat, on the other hand, as was shown independently and almost simultaneously by Cushny (20), by Kehrer (21), and by myself (22), the uterine tone and contractions are inhibited in the non-pregnant, stimulated in the pregnant animal, by sympathetic nerves or supra-renal preparations. I regard it, then, as of great significance that in the uterus of the cat, as well as in that of the dog, the guinea-pig, the rat, and the rabbit, I have always observed, in all functional conditions, powerful tonic contraction as the effect of applying pituitary extract. The results were obtained by intravenous injection into the anaesthetised or brainless animal, and also by Kehrer's method of adding the extract to a bath of warm oxygenated Ringer's solution, in which the isolated horn of the uterus was so suspended as to pull on a recording lever. The effect, under these conditions of adding a few drops of pituitary extract to the 200 c.c. of Ringer's solution in the bath, is illustrated in figs. 3 and 4. So little, in my experience, is the effect dependent on the condition of the uterus as regards oestrum or pregnancy, that the uterus of a virgin, half-grown cat responded to the pituitary extract by as marked a tonic contraction as was given by any of the numerous pregnant or multiparous organs examined.

The effect of pituitary extract on the uterus, then, shows again the absence of parallelism to the effects of sympathetic nerves, the effect of the extract being always tonic contraction, even when stimulation of the hypogastric nerves produces pure inhibition of tone and rhythm.

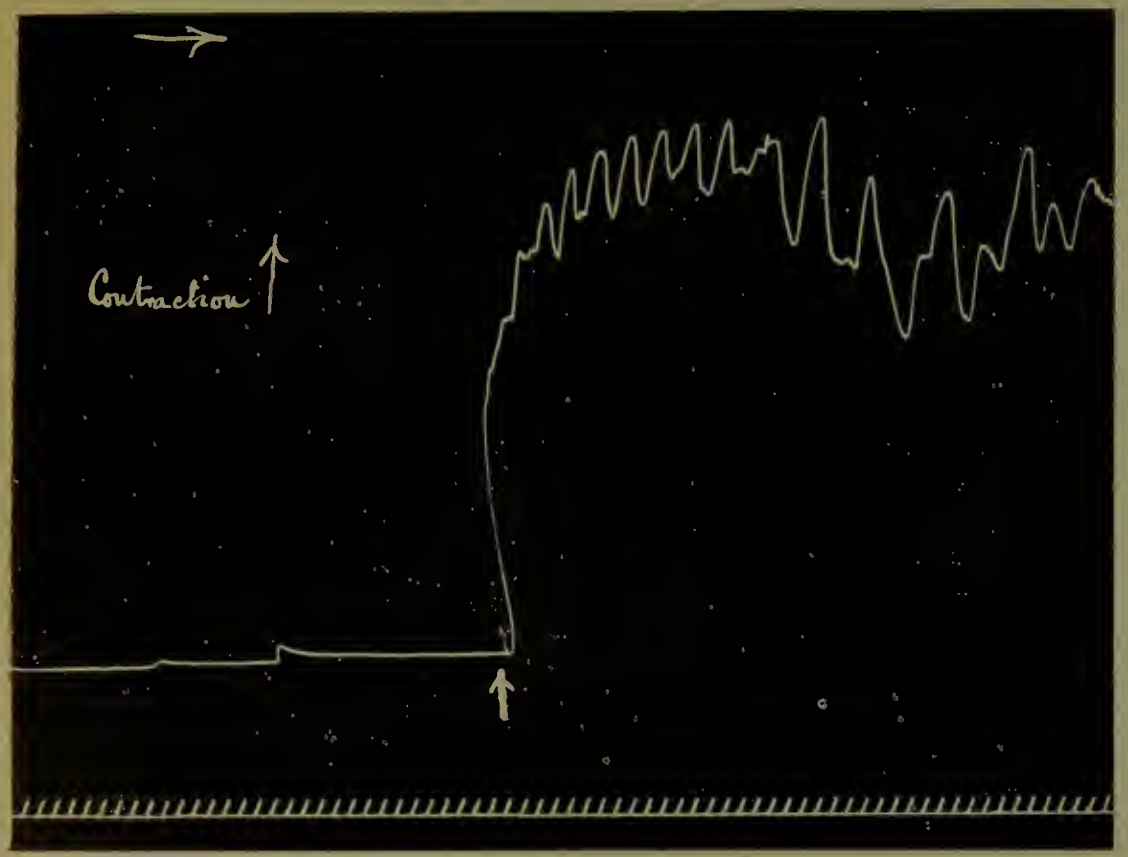

Figure 4.—A record, similar to that of Fig. 3, from the uterus of a pregnant guinea-pig. At ↑ 3 drops of pituitary extract were added to the bath. Scale, ½ linear.

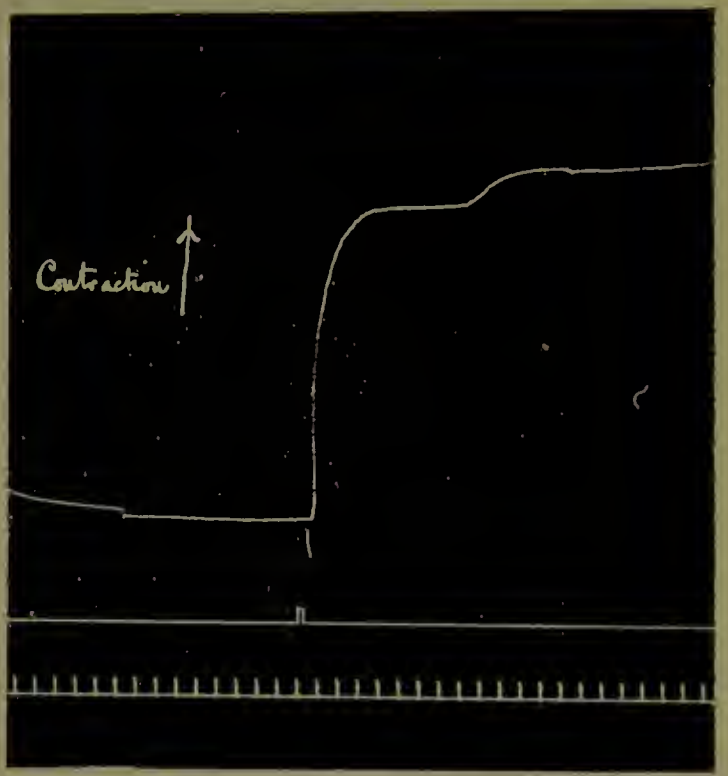

Figure 5.—Isolated retractor penis of the dog. Effect of adding 0·5 c.c. pituitary extract to the bath. Scale, ½ linear.

IV. Other Organs Containing Plain Muscle

The intestines and the urinary bladder give no such marked response to the pituitary extract as the organs hitherto mentioned. In a dog anaesthetised with A.C.E. mixture I observed, indeed, a distinct inhibition of intestinal movements when the extract was given intravenously, even when the splanchnic nerves were cut. This might be regarded as indicating a similarity of action to sympathetic nerves. An isolated loop of intestine, however, the rhythm and tone of which are immediately inhibited by adrenaline, contracts, though but feebly, when pituitary extract is added to the bath. It is probable, therefore, that the inhibition, seen under normal conditions of circulation, is due to the intense anaemia which the vaso-constrictor action of the extract produces.

The bladder of the cat, when the extract is injected intravenously, usually exhibits a temporary weakening, followed by more prolonged increase of tone. Neither is of any great extent. A guinea-pig's bladder, suspended in the Ringer-bath, contracted feebly when pituitary extract was added.

The plain muscular coats of the intestines and the bladder contract, then, like other plain muscle, in response to pituitary extract, but their sensitiveness thereto is small in comparison to that of some organs. The retractor penis of the dog, a convenient sheet of plain muscle for examination in the Ringer bath, contracts, as might be expected, when the extract is added (fig. 5).

No effect could be detected on pilo-motor muscles or on the mammalian pupil.

V. Gland Cells

Schäfer and Herring found that the extract caused secretion neither of saliva nor pancreatic juice, which observations I have confirmed. In its failure to evoke salivary secretion the extract is again contrasted to adrenaline. The profuse flow of urine which the extract causes, as first shown by Schäfer, in conjunction with Magnus (13) and with Herring (3), can hardly be regarded as a true glandular secretion.

VI. The Action after Ergotoxine

I have shown (23) that the specific ergot alkaloid ergotoxine, when injected intravenously in certain doses, annuls all motor effects of sympathetic nerves and adrenaline, so that the latter produces, in the cat,

a fall of blood-pressure and relaxation of the pregnant uterus in place of the customary rise and contraction. Ergotoxine may be given, however, in any quantity without affecting the contraction of arterial and uterine muscle produced by a subsequent injection of pituitary extract (fig. 6).

Action of Enzymes, etc., on the Extract

Schäfer and Herring (5) state that peptic digestion reduces the action of the extract on the blood-pressure without affecting the action on the kidney, but that neither action is affected by tryptic digestion. They also obtained results which they regarded as indicating that oxidation by H_2O_2 destroys the pressor action more quickly than the diuretic action. Certain obvious precautions seem to have been omitted: there is no indication that they controlled the activity of their enzymes or the response of their animal. A negative result should obviously not be accepted as indicating destruction of the agent unless a positive effect could subsequently be obtained with the untreated extract. Adopting these precautions I have failed to confirm them on all points. Digestion for twenty-four hours with a peptic extract of proved activity and 0·2 per cent. HCl failed to alter in any perceptible degree the pressor or diuretic action of my extract. I can only conclude that the peptic extract used by Schäfer and Herring contained some antagonistic depressor substance, or that their animal was for some reason unresponsive to the pressor effect. On the other hand every active preparation of trypsin which I have tried has reduced the action on the blood-pressure and on the urinary flow practically to *nil* after a few hours' digestion. Commercial trypsin, 'liquor pancreaticus,' pure pancreatic juice obtained by secretin and activated by enterokinase—all gave the same result. In all cases a subsequent injection of the original extract produced the usual rise of blood-pressure and acceleration of the flow of urine (figs. 7 and 8). It may be suggested, in the absence of evidence for control on that point, that Schäfer and Herring were using an inactive preparation of trypsin: at least it is clear that the tryptic preparations used by me contained something which was not present in theirs. In my experience oxidation with H_2O_2 failed likewise to discriminate between the pressor and diuretic activities. Both effects were smaller after oxidation than those produced by a subsequent injection of the original extract; but that either had suffered greater change than the other was not apparent.

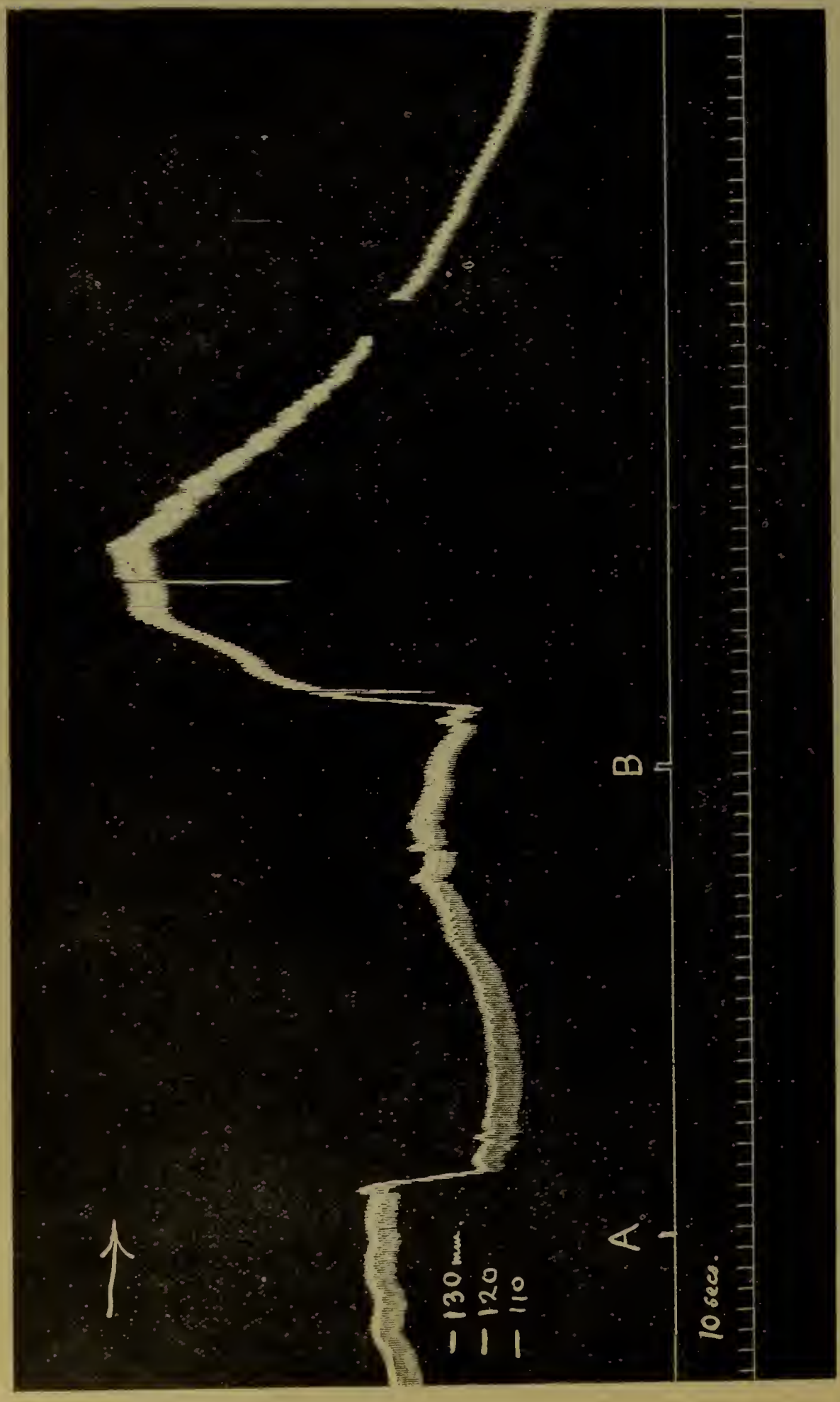

Figure 6.—Carotid blood-pressure of pithed cat. 5 mgms. ergotoxine phosphate injected previously. Injections:
At A—0·1 mgm. adrenaline.
At B—2 c.c. pituitary extract.
Scale, ½ linear.

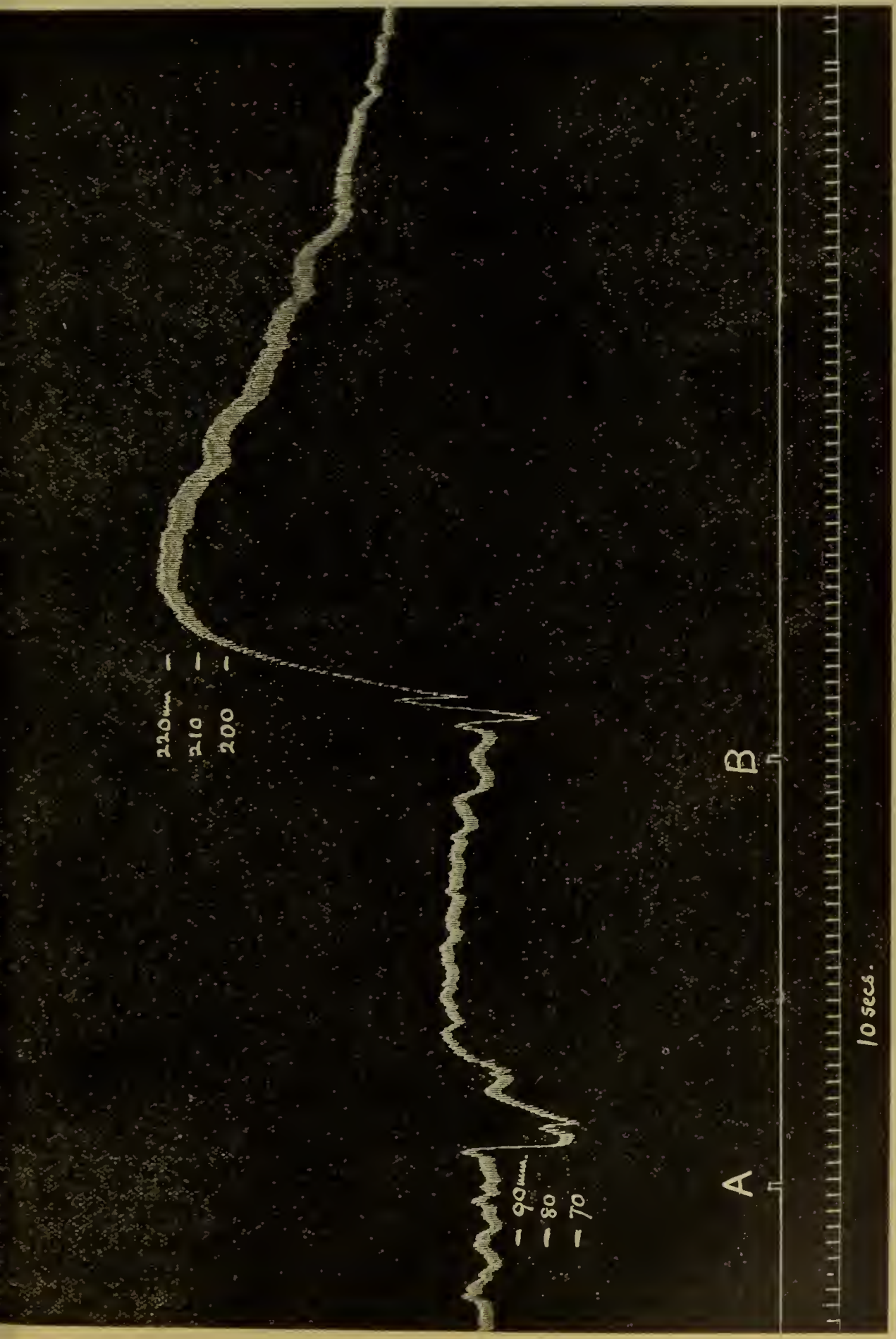

Figure 7.—Carotid blood-pressure of pithed cat. Intravenous injections:
At A—2 c.c. pituitary extract digested with trypsin and 1 % Na_2CO_3 for eighteen hours
At B—2 c.c. of the same extract digested for the same time with the same amount of trypsin *previously boiled* and 1 %, Na_2CO_3.
Scale, ½ linear.

Figure 8.—Carotid blood-pressure and drop-record of urine (bladder cannula) of cat (ether). [Injections as in Fig. 7:
At A—1 c.c. extract digested with trypsin.
At B—1 c.c. extract incubated with boiled trypsin.
Scale, ½ linear.

Excretion. Attempt to Produce Immunity

The fact, discovered by Howell, that second doses are relatively ineffective, suggests that the active principle is not readily destroyed or rendered inactive in the body. I found that the urine of a cat, excreted in response to an injection of the extract, had a pressor action, like a dilution of the extract, when tested on another cat (fig. 9). Probably the active principle, therefore, is at least to some extent excreted unchanged.

The refractory state to further injections has nothing to do with a true 'immune' reaction. In the serum of a rabbit, treated for a month with increasing injections of the extract, I could distinguish no trace of a body neutralising the physiological activities of the extract.

Discussion of the Results

It is clear from the foregoing that the characteristic action of extracts of the posterior lobe of the pituitary body is stimulation of plain muscle fibres. Different organs containing plain muscle show a varying sensitiveness of response to the extract, the arteries, the uterus and the spleen being conspicuously affected. This unequal distribution of effect cannot, however, in any way be related to inequalities of innervation by nerves of the true sympathetic or of the autonomic system as a whole. Ergotoxine, which excludes motor effects of true sympathetic nerves, and of drugs acting through those nerves or like them, leaves the action of pituitary extract intact. Neither atropine nor curare affects its direct action in any degree. The muscle of the mammalian heart is possibly affected to some extent by the extract, apart from effects secondary to constriction of the coronary arterioles: Herring's observations on the frog's heart render this most probable. No effect could be detected on the response of voluntary muscles, either to direct or indirect stimulation. The active principle is then essentially a stimulant of involuntary, and especially of plain muscle.

The question of the diuretic effect needs some further discussion. Houghton and Merrill (24) have recently taken the somewhat extreme view that this is entirely secondary to the rise of blood-pressure. They state that the rise of blood-pressure produced by adrenaline is accompanied by a similar diuresis. This latter observation is directly opposed to the experience of others, and I have never myself been able to confirm it. Further it was shown quite clearly by Schäfer and Herring that a second injection of pituitary extract may cause distinct

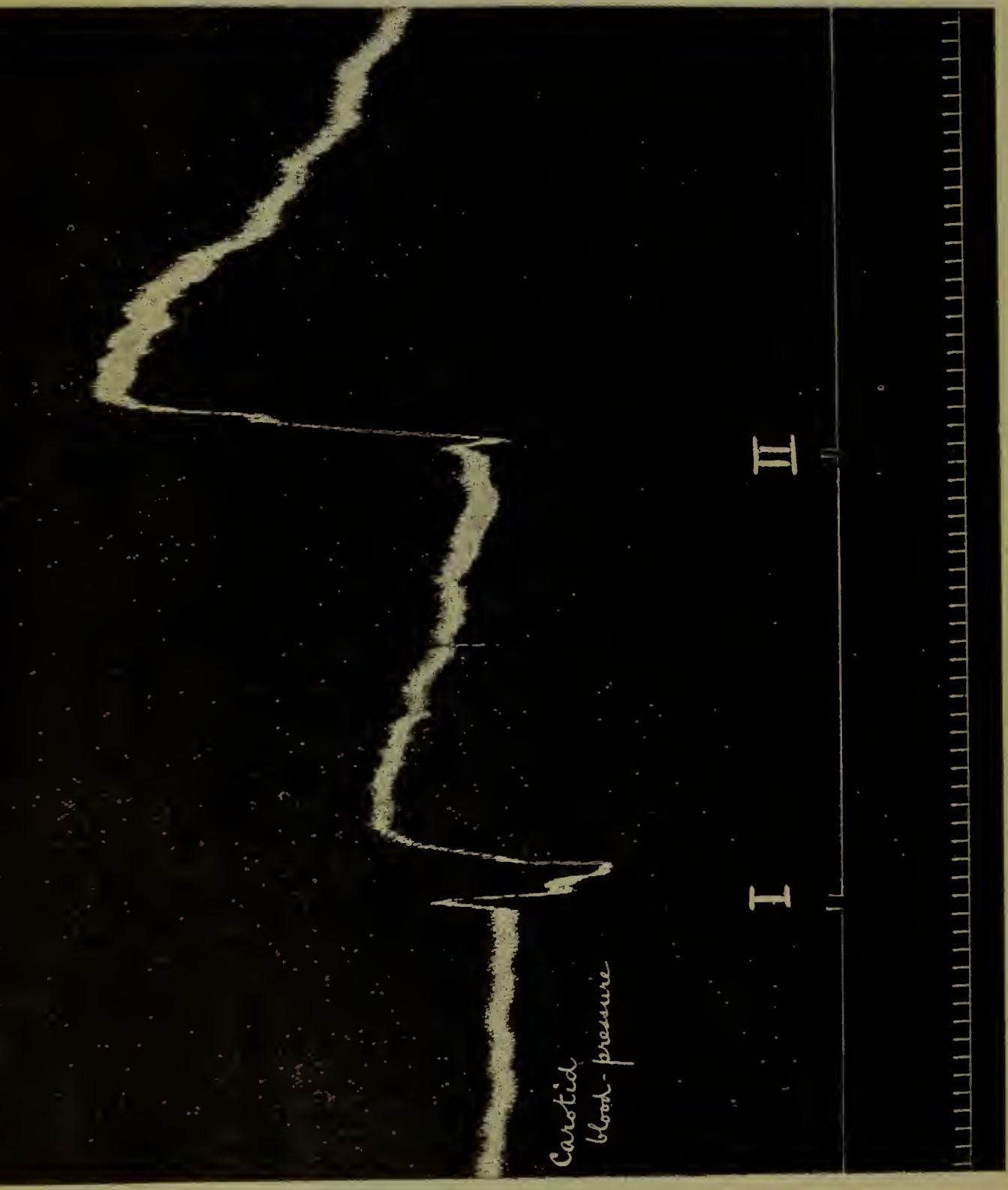

Figure 9.—Carotid blood-pressure of pithed cat. Intravenous injections:
At I.—8 c.c. of normal cat's urine.
At II.—8 c.c. of urine collected after injection of 4 c.c. pituitary extract. (50 c.c. in all collected during 2 hours).

diuresis without any perceptible rise of blood-pressure. While such an observation, which I have been able repeatedly to confirm, sufficiently disproves the statement that the diuresis is secondary to and runs parallel to the actual rise of systemic pressure, it does not remove the possibility of the dependence of the diuresis on vascular effects. A redistribution of the blood in the system, caused by the comparative irresponsiveness of the renal arterioles, is conceivable without actual rise of general systemic pressure, especially if the arterial constriction is accompanied by weakening of the heart's action, due to the depressor constituent which the extract always contains, the action of which, moreover, is much more evident in the case of a second injection.

The differential action of enzymes and oxidation on the supposed pressor and diuretic principles, alleged by Schäfer and Herring, has not been confirmed in my experiments. On the contrary I have found that whatever destroyed one action destroyed both. Their other evidence for the existence of two principles seems to me also inadequate. They lay stress on the difference in the time relations between the two effects and the relatively greater effect of second injections on diuresis. The difference in time-relations of a diuretic and pressor effect is, however, a familiar phenomenon in cases where there can be no question of the presence of more than one active principle. If strophanthin, for example, be injected intravenously into a dog or cat, the immediate effect on the diuresis is usually a distinct retardation: later, as the rise of arterial blood-pressure passes off, there is generally a secondary acceleration which often persists after the blood-pressure has regained its original level. A similar sequence of events was recently observed by P. P. Laidlaw and myself in experiments, in course of publication, on the action of a pure, crystalline active principle from Apocynum. Such a difference in time-relations cannot, therefore, be accepted as necessitating the presence of two principles. The relatively greater efficacy of a second injection in causing diuresis as compared with its pressor effect can also be interpreted in another way, as indicated above. The blood-pressure tracing is complicated by the presence of the heart-depressing principle: it is not a fair index of the degree of vaso-constriction in this instance. An apparently greater relative efficacy of second injections can also be observed in the case of the uterus, when the effect on that organ is compared with that on the arterial pressure. I have frequently seen, as the result of a second injection, marked contraction of the uterus accompanying a very slight or no rise of blood-pressure.

It does not seem justifiable, however, to draw from this observation the conclusion that the principle acting on the plain muscle of the uterus is different from that which acts on the plain muscle of the arteries. It is, of course, true that nothing short of the isolation of a single pure principle, producing both pressor and diuretic effects, would make the view that two principles exist untenable. While awaiting further evidence, however, the conception of both effects as due to one principle seems to me adequate and simpler.

Conclusions

1. The action of extracts of the posterior lobe of the pituitary body is a direct stimulation of involuntary muscle, without any relation to innervation. The action is most nearly allied to that of the digitalis series, but the effect on the heart is in this case slight, that on plain muscle intense.

2. The active principle is excreted in the urine.

3. No true immune reaction is produced by repeated injections of the extract.

4. The evidence advanced in proof of the existence of separate pressor and diuretic principles is inadequate.

REFERENCES

1. Oliver and Schäfer, *Journ. of Physiol.*, XVIII, p. 277, 1895.
2. Herring, *Journ. of Physiol.*, XXXI, p. 429, 1904.
3. Cramer, *Quart. Journ. of Exper. Physiol.*, I, p. 189, 1908.
4. Bell and Hick, *B.M.J.*, 1909 (I), p. 777.
5. Schäfer and Herring, *Phil. Trans.*, 1906.
6. Langley, *Journal of Physiol.*, XXVII, p. 237, 1901.
7. Brodie and Dixon, *Ibid.*, XXX, p. 476, 1904.
8. Elliott, *Ibid.*, XXXII, p. 401, 1905.
9. Meyer, *Zeitschr. f. Biol.*, XLVIII, 1906.
10. Langendorff, *Zentralbl. f. Physiol.*, XXI. p. 551, 1907.
11. De Bonis and Susanna, *Zentralbl. f. Physiol.*, XXIII, p. 169, 1909.
12. Maas, *Pflüger's Arch.*, LXXIV, p. 281, 1899.
13. Dogiel and Archangelsky, *ibid.*, CXVI., p. 482, 1906.
14. Schäfer, *Arch. de Sci. biol. de St. Petersbourg* (*Pawlow Festschrift*), p. 251, 1904.
15. Wiggers, *Amer. Journ. of Physiol.*, XXIV, p. 391, 1909.
16. Pal, *Wien med. Wochenschr.*, No. 3, 1909.
17. Hedborn, *Skand. Arch. f. Physiol.*, VIII., 1898.
18. Cleghorn, *Amer. Journ. of Physiol.*, II, p. 273, 1899.
19. Schäfer and Magnus, *Journ. of Physiol.*, XXVII. p. ix (*Proc. Phys. Soc.*).
20. Cushny, *Journ. of Physiol.*, XXXV, p. 1, 1906.
21. Kehrer, *Arch. f. Gynäkol.*, LXXXI, p. 160, 1906.
22. Dale, *Journ. of Physiol.*, XXXIV, p. 163, 1906.
23. Barger and Dale, *Bio-Chem. Journal*, II, p. 240, 1907.
24. Houghton and Merrill, *Journ. of the Amer. Med. Assoc.*, LI, p. 1849, 1908.
25. Howell, *Journ. of Exper. Med.*, III, p. 2, 1898.